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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

HUNNICUTT, RACHEL KAPUST

ART UNIT PAPER NUMBER

1647

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/865,291	Applicant(s) TSIEN ET AL.	
	Examiner Rachel K. Hunnicutt	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 June 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 95, 106, 108, 109, 115-119, 121, 125, 128, 130, 131 and 145-162 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 95, 106, 108, 109, 115-119, 121, 125, 128, 130, 131 and 145-162 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>0802</u> . | 6) <input type="checkbox"/> Other: _____ |

RESPONSE TO AMENDMENT

Applicant's amendment filed June 1, 2004 is acknowledged. Claims 1-94, 96-105, 107, 110-114, 120, 122-124, 126-127, 129, and 132-144 have been canceled. Claims 95, 109, 115, 118, 119, 121, 125, 128, 147, 150, 153, 154, 156-158, 160, and 162 are amended. Claims 95, 106, 108, 109, 115-119, 121, 125, 128, 130, 131, and 145-162 are pending and under consideration. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections/Objections Withdrawn

The objection to the specification regarding the use of trademarks is withdrawn in response to Applicants' amendments to the specification.

The rejection of claims 95, 106, 108, 109, 115-119, 121, 125, 128, 130, 131, 145, 146, 149-156, and 161-163 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in response to Applicants' amendments to the claims. The rejection of claims 110-114 and 120 is withdrawn in view of the cancellation of these claims.

The rejection of claim 108 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention is withdrawn in response to Applicants' amendment to the claim.

The rejection of claims 147, 148, and 153-160 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention is withdrawn in response to Applicants' amendments to the claims.

The rejection of claims 150-152, 154-156, and 158-160 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

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subject matter which applicants regard as the invention is withdrawn in response to Applicants' amendments to the claims.

The rejection of claims 147-149, 153, and 157 under 35 U.S.C. 102(e) as being anticipated by Craig *et al.* (U.S. Patent No. 6,656,696) is withdrawn because Craig *et al.* no longer anticipate the claims. Craig *et al.* do not teach a fluorescent protein having a reduced tendency to oligomerize.

The rejection of claims 150-152, 154-156, and 158-160 under 35 U.S.C. 103(a) as being unpatentable over Craig *et al.* is withdrawn because it would not be obvious to one of ordinary skill in the art to utilize a fluorescent protein having a reduced tendency to oligomerize.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 95, 106, 108, 109, 119, 130, 131, 145, and 146 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claim 95, as amended, is drawn to a polynucleotide encoding a chimeric indicator having "portions". It is not clear from either the claim or the specification what the portions are meant to encompass. Claims 106, 108, 109, 119, 130, 131, 145, and 146 are rejected as being dependent on claim 95. The rejection could be obviated by wording the claim in way similar to claim 147, *i.e.* "A polynucleotide encoding a chimeric phosphorylation indicator having portions comprising a phosphorylatable polypeptide and a fluorescent protein".

Claims 115-118, 121, 125, 128, and 147-162 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claim 147, as amended, is drawn to a polynucleotide encoding a fluorescent protein which is non-oligomerizing and it has a reduced

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tendency to oligomerize. A protein cannot be non-oligomerizing while at the same time still form oligomers. One of skill in the art would not know whether the claimed fluorescent proteins never form oligomers or if they do occasionally. Claims 115-118, 121, 125, 128, and 148-162 are rejected as being dependent on claim 147.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 95, 106, 109, 115-119, 121, 125, 128, 130, 131, and 145-162 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding a fluorescent protein with a reduced tendency to oligomerize, wherein the protein is GFP or a fluorescent protein related to GFP and the amino acid sequence has the mutation A206K, L221K, and or F223R, does not reasonably provide enablement for a polynucleotide encoding any fluorescent protein having a reduced tendency to oligomerize. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention; 2) state of the prior art; 3) relative skill of those in the art; 4) level of predictability in the art; 5) existence of working examples; 6) breadth of claims; 7) amount of direction or guidance by the inventor; and 8) quantity of experimentation needed to make and/or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 95, 106, 109, 115-119, 121, 125, 128, 130, 131, and 145-162 encompass polynucleotides encoding fluorescent proteins having a reduced tendency to oligomerize. However, the specification only discloses two means for engineering such polynucleotides: (a) having two of the same fluorescent protein in tandem so that intramolecular homodimers are formed; and (b) having one or more of the mutations A206K, L221K, and F223R in GFP or GFP related proteins. The specification does not provide examples of other mutations at these

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residues which would be sufficient for reducing the tendency to form oligomers, nor does the specification provide examples of other mutations at other residues which would be successful.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions.

Due to the large quantity of experimentation necessary to generate the number of variants recited in the claims and screen the same for the tendency to form oligomers, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claims 95, 106, 109, 115-119, 121, 125, 128, 130, 131, and 145-162 are newly rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to a genus, *i.e.* polynucleotides encoding fluorescent proteins having a reduced tendency to oligomerize. Applicants have disclosed two species of such polynucleotides: (a) polynucleotides having two of the same fluorescent protein in tandem so that intramolecular homodimers are formed; and (b) polynucleotides having one or more of the mutations A206K, L221K, and

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F223R in GFP or GFP related proteins. However, Applicants have not disclosed sufficient species for the broad genus of any fluorescent protein having a reduced tendency to oligomerize.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses hundreds of different polynucleotides encoding proteins with varying structures and functions. A description of a genus of polynucleotides encoding polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, said features constituting a substantial portion of the genus. The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, the disclosure of polynucleotides having two of the same fluorescent protein in tandem so that intramolecular homodimers are formed and polynucleotides having one or more of the mutations A206K, L221K, and F223R in GFP or GFP related proteins is insufficient to describe the genus. Therefore, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Conclusion

NO CLAIMS ARE ALLOWED.

The following articles, patents, and/or published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

Pollard *et al.* (2002), *Ann. N.Y. Acad. Sci.* 971: 617-619

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel K. Hunnicutt whose telephone number is (571) 272-0886. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RKH
8/19/04


JANET ANDRÉS
PRIMARY EXAMINER